R E M A R K S

Request for Form PTO-892

JP 2002-201126 was applied in a prior art rejection in the August 29, 2007 Office Action.

The Examiner is respectfully requested to make JP 2002-201126 of record by citing JP 2002-201126 on a Form PTO-892.

Claim Amendments and New Claims

Claim 3 was amended by including features of original claims 7 and 10.

Claim 12 was amended by including features of original claims 3 and 10.

New claim 14 includes the feature of original claim 4.

New claim 15 is supported in the specification on page 6, line 6.

New claim 16 is supported in the specification on page 8, lines 30 to 33; page 9, lines 2 and 3; and page 9, lines 24 to 28.

New claim 17 is supported in the specification on page 9, last line.

New claim 18 is supported in the specification on page 9, lines 33 to 35 and page 12, line 12.

Rejection Under 35 USC 101

Claim 13 was rejected under 35 USC 101 for claiming a "use" without setting forth any steps involved in the process (see item no. 2 on page 2 of the Office Action).

Claim 13 was canceled hereinabove.

Withdrawal of the 35 USC 101 rejection is therefore respectfully requested.

Anticipation Rejection Under 35 USC 102

Claims 1 to 6, 8, 9, 12 and 13 were rejected under 35 USC 102 as being anticipated by WO 02/14280 to Nakai et al. for the reasons set forth in item no. 4 on page 3 of the Office Action. The Examiner's reasons for the rejection refer to EP 1 308 440, a family member of WO 02/14280.

Claims 7 and 10 were not included in the 35 USC 102 rejection. The features of original claim 7 (eye drop) and claim 10 (0.01 to 1% w/v) are included in the present claims.

Nakai et al. do not teach or suggest an eye drop, an amount of the compound being 0.01 to 1% w/v or the treatment of pruritus.

Withdrawal of the 35 USC 102 rejection is therefore respectfully requested.

Obviousness Rejection Under 35 USC 103

Claims 1 to 13 were rejected under 35 USC 103 as being unpatentable over WO 02/14280 to Nakai et al. in view of USP 5,756,508 to Thompson et al. and further in view of JP 2002-201126 to Noyori et al. for the reasons set forth in item no. 8 beginning at the bottom of page 4 and continuing to the middle of page 6 of the Office Action.

It was admitted in the Office Action that Nakai et al. is deficient in using the piperidine compound in eye drops.

The position was taken in the Office Action that it would have been obvious to make a dosage form in the form of eye drops using the compound disclosed by Nakai et al. and to adjust the correct dose as disclosed by Nakai et al. based on the combined teachings of Nakai et al. and Thompson et al. It is respectfully

submitted that in applicants' present claims which recite a concentration of an eye drop comprising 0.01 to 1% (w/v) of the compound recited in applicants' claims distinguish over the references for the following reasons.

Adjustment of the concentration of the active ingredient contained in an eye drop is generally determined in consideration of the physical properties, pharmacological effects and the like of the compound. The piperidine compound disclosed by Thompson and the compounds recited in applicants' present claims have only one chemical structure in common, which is the piperidine ring. Moreover, the main action of the compound of Thompson et al. and that of the compound recited in applicants' present claims are different from each other (muscarinic agonist for the former and PDE4 inhibitor for the latter).

Whereas applicants' present claims recite a selective eye drop concentration range of 0.01 to 1% (w/v), Thompson et al. disclose merely a broad eye drop concentration range of 0.1 to 4%. Accordingly, the eye drop concentration range of Thompson et al. include eye drop concentrations which fall outside of applicants' claimed range. Stated differently, Thompson et al.

have no teaching or suggestion for an eye drop concentration as low as 0.01 % as recited in applicants' claims and as set forth in applicants' Examples. Such low eye drop concentration as claimed by the applicants provide an excellent antipruritic effect (see Table 1 on page 11 of applicants' specification).

In addition to the above argument, attention is directed to the enclosed copy of the drug package insert of "TRAVATAN (TRAVOPROST OPHTHALMIC SOLUTION) 0.004%." According to the information provided in the drug package insert, TRAVATAN is a commercially available pharmaceutical product having a concentration of 0.004% which is lower than the range of concentration of the eye drop disclosed by Thompson et al.

Further, an eye drop at a concentration of 0.01 to 1% (w/v) is outside the range of the parenterally administered dosage disclosed by Nakai et al. (1 to 100 mg), since the volume of an eye drop is generally at most 50 µl.

More specifically, the unit of concentration used in the present specification, w/v %, expresses the weight (g) of the active ingredient per 100 mL of solution. The maximum volume of an eye drop actually administered into an eye is considered to be

at most 50 μL, since one drop of an eye drop generally contains 50 μL. Accordingly, when 1 mg/50 μL is expressed in w/v %, it is 2 g/100 mL, i.e., 2 w/v %. In contrast, 1 w/v %, which is the maximum dose for applicants' presently claimed eye drop, is calculated to contain 0.5 mg of active ingredient in a volume of 50 μL. Therefore, even the maximum dose of applicants' present claims (0.5 mg) is outside the range of the parenterally-administered dose disclosed in Nakai et al. (1 to 100 mg).

Therefore, it is respectfully submitted that a person of ordinary skill in the art would encounter a difficulty in arriving at the appropriate concentration of the active ingredient in an eye drop as recited in applicants' claims in view of the pharmacological effects and other factors to be taken into consideration.

Further, it is respectfully submitted that it is not obvious based on the combined teachings of Nakai et al. and Thompson to find that 0.01 to 1% (w/v) is the optimal eye drop concentration of the compound recited in applicants' claims.

It was admitted in the Office Action that Nakai et al. and Thompson et al. are deficient in disclosing a combination of

piperidine and other drugs that treat an eye allergy as required by applicants' claim 11.

JP 2002-201126 to Noyori et al. was cited for disclosing eye drops for alleviating the unpleasant irritant eye ache at the time of instillation induced by sodium cromoglycate and enhancing immediate antipruritic effects which an antihistaminic agent possesses (see the English-language abstract of JP 2002-201126).

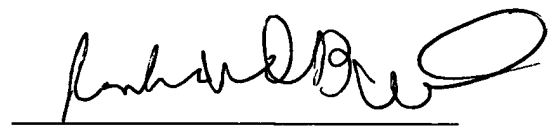
To expedite the prosecution of the application, claim 11 was canceled hereinabove.

It is therefore respectfully submitted that applicants' present claims are not anticipated and are not rendered obvious over the references, either singly or combined in the manner relied upon in the Office Action in view of the many distinctions discussed hereinabove. Withdrawal of each of the 35 USC 102 and 35 USC 103 rejections is respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Encs.: (1) PETITION FOR EXTENSION OF TIME

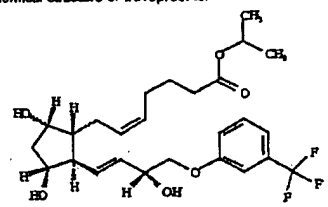
(2) copy of package insert for "TRAVATAN"

TRAVATAN® Z
(travoprost ophthalmic solution) 0.004%

Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is [1*R*-[1α(*Z*),2β(1*E*,3*R**),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.55. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile,methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN® Z ophthalmic solution is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/Kg. Each mL of TRAVATAN® Z contains: Active: travoprost 0.004%. Inactives: polyoxyl 40 hydrogenated castor oil, sorbitol, (boric acid, propylene glycol, sorbitol, zinc chloride), sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water, USP. Preserved in the bottle with an ionic buffered system.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing trabecular meshwork and uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption:

Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/mL (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma C_{max} was 0.018 ± 007 ng/mL (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating that there was no significant accumulation.

Metabolism:

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Elimination:

The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

Clinical Studies

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25–27 mm Hg, who were treated with TRAVATAN® (travoprost ophthalmic solution) or TRAVATAN® Z (travoprost ophthalmic solution) dosed once-daily in the evening demonstrated 7-8 mm Hg reduction in intraocular pressure. In subgroup analysis of this study, mean IOP reduction in black patients was up to 1.8 mm Hg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24-26 mm Hg on TIMOPTIC® 0.5% BID who were treated with travoprost 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID demonstrated 6-7 mm Hg reductions in intraocular pressure.

Travoprost ophthalmic solution, 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

INDICATIONS AND USAGE

TRAVATAN® Z ophthalmic solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

TRAVATAN® Z is contraindicated in patients with hypersensitivity to travoprost or any other ingredients in this product.

WARNINGS

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of prostaglandin analogues, including travoprost ophthalmic solution, 0.004%.

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see **Information for Patients**).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see **WARNINGS**). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

TRAVATAN® Z ophthalmic solution should be used with caution in patients with a history of intraocular

inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® Z should be used with caution in these patients.

TRAVATAN® Z has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

Information for Patients
Patients should be advised concerning all the information contained in the Warnings and Precautions sections. Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day did not show any evidence of carcinogenic potential. However, at 100 µg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 µg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 µg/kg, based on plasma active drug levels.

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day [250 times the maximum recommended human ocular dose of 0.04 µg/kg/day on a µg/kg basis (MRHOD)]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects
Pregnancy Category: C
Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 µg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly.

Travoprost was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1.0 µg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD). In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥ 0.12 µg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies in pregnant women. TRAVATAN® Z should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® Z ophthalmic solution is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS
The most common adverse event observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN® Z (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to subconjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN® Z included abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, corneal staining, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at an incidence of 1 to 5% in these clinical studies were accidental injury, allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® Z ophthalmic solution should not exceed once-daily since it has been shown that more frequent administration of travoprost may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration of travoprost. The maximum effect is observed 12 hours after administration and is maintained throughout the day.

TRAVATAN® Z may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED
TRAVATAN® Z (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system.

TRAVATAN® Z is supplied as a 2.5 mL solution in a 4 mL and a 5 mL solution in a 7.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 mL fill in 4 mL bottle	NDC 0065-0260-25
5 mL fill in 7.5 mL bottle	NDC 0065-0260-05

Storage: Store at 2° - 25°C (36° - 77°F).

Rx Only

U.S. Patent Nos. 5,889,052 and 6,235,781

* TIMOPTIC is the registered trademark of Merck & Co., Inc.

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